Effects of Coronavirus Disease 2019 (COVID-19) Pandemic on Antimicrobial Prevalence and Prescribing in a Tertiary Hospital in Singapore

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Research

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Abstract

Background: The deployment of antimicrobial stewardship (AMS) teams to deal with the COVID-19 pandemic can lead to a loss of developed frameworks, best practices and leadership resulting in adverse impact on antimicrobial prescribing and resistance. We aim to investigate effects of reduction in AMS resources during the COVID-19 pandemic on antimicrobial prescribing and resistance.

Methods: One of 5 full-time equivalent AMS pharmacists was deployed to support pandemic work and AMS rounds with infectious disease physicians were reduced from 5 to 2 times a week. A survey in acute inpatients was conducted using the Global Point Prevalence Survey methodology in July 2020 and compared with those in 2015 and 2017-2019.

Results: The prevalence of antimicrobial prescribing (55% in 2015 to 49% in 2019 and 47% in 2020, $p = 0.02$) and antibacterials (54% in 2015 to 45% in 2019 and 42% in 2020, $p < 0.01$) have been reducing despite the pandemic. Antimicrobial prescribing in infectious disease wards with suspected or confirmed COVID-19 cases was 29% in 2020. Overall, antimicrobial prescribing quality indicators continued to improve (e.g. reasons in notes, 91% in 2015 to 94% in 2019 and 97% in 2020, $p < 0.01$) or remained stable (compliance to guideline, 71% in 2015 to 62% in 2019 and 73% in 2020, $p = 0.08$).

Conclusion: AMS efforts over the years paid dividends during the COVID-19 pandemic to sustain the control of antimicrobial prevalence and quality of AMU in non-COVID-19 wards and plausibly also in COVID-19 wards.

Background

The global response to the coronavirus disease 2019 (COVID-19) pandemic has focused on controlling the spread of infection and development of treatment and vaccines.[1] The typical symptoms of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are fever, sore throat, fatigue, cough or dyspnea.[2] These symptoms may prompt clinicians to start antibiotics to treat community-acquired pneumonia or COVID-19 with secondary bacterial infection. In a review of patients with coronavirus infections, 62/806(8%) of patients with COVID-19 were reported to have bacterial or fungal co-infections. However, among COVID-19 patients, 1450 of 2010 (72%) received antibiotics. These agents tended to be broad-spectrum and empiric.[3] As the pandemic continues, treatment of patients with respiratory symptoms can drive increasing rates of empiric antimicrobial therapy.

Antimicrobial stewardship (AMS) teams generally comprise infectious disease physicians, AMS pharmacists or pharmacists with special interest in infectious diseases. Many of these individuals are re-deployed to focus on patient care and other areas directly related to COVID-19 during the pandemic. This can lead to loss of established AMS frameworks, best practices, and leadership in healthcare institutions, resulting in adverse impact on antimicrobial resistance in the long term.[4] It is important that healthcare systems keep AMS in consideration as they channel resources to control COVID-19.[5]

The Global Point Prevalence Survey (Global-PPS) first conducted in 2015 provides a rapid way to understand the quantity and quality of antimicrobial prescribing.[6] Using a standardised methodology over the years, the surveys allow comparisons to be made between time periods.[7] Information from these surveys can be used for tailor made surveillance and help develop prescribing guidelines and educational initiatives to improve antimicrobial use. The antimicrobial stewardship team at Tan Tock Seng Hospital (TTSH) and the National Centre for Infectious Diseases (NCID), Singapore, comprise a team of 5 full-time equivalent (FTE) pharmacists who provided daily prospective review and feedback (PRF) on piperacillin-tazobactam, carbapenem and ciprofloxacin use. They work closely with a team of 5 Infectious diseases (ID) physicians who take turns to perform PRF on complex cases. Since the start of the pandemic in January 2020, 1 full-time equivalent of AMS pharmacist was deployed to support COVID-19 clinical trials and only 1–2 ID physicians continued with PRF once to twice a week. The other ID physicians were deployed to duties related to the pandemic. In this study, we aimed to compare the prevalence of antimicrobial use and quality indicators in hospitalised patients using the Global-PPS methodology from 2015 and 2017–2020 to investigate the effects of the deployment of AMS manpower resources to support the ongoing COVID-19 efforts.

Methods

Study design, setting and patients

This was a retrospective study comparing 5 cross-sectional surveys conducted in years 2015, 2017, 2018, 2019 and 2020. The survey methodology was in accordance with Global-PPS study protocol in 2015 and 2017–2020. They were conducted in acute care wards of TTSH, a 1500-bed university teaching adult hospital in Singapore, in the 5 years. The new 330-bed NCID, located in the same campus, was included in years 2019 and 2020. AMS pharmacists conducted all Global-PPS in the 2 institutions.

Global-PPS was conducted on any day except weekends and public holidays. The 5 surveys were conducted in March 2015, November 2017, October 2018, April 2019 and July 2020. All patients in inpatient wards were included for audit at 0800 hours of the chosen survey day. Following the Global PPS annual protocols, antimicrobials for topical use were excluded. Data collection was completed using the Global-PPS methodology specified forms. The ward form included the total number of admitted inpatients at 0800 hours on survey day and the total number of available inpatient beds in the surveyed wards. The patient form was only completed if patient included in the survey was on at least 1 systemic antimicrobial at 0800 hours on survey day. Patient data was collected using electronic medical records. No patient identifier was collected. The survey was completed without questioning the diagnoses indicated by primary teams. The type of data collected were described previously (https://www.global-pps.com/).[6] Specifically, age, ward type, type of antimicrobial, diagnosis, type of indication (i.e. whether prophylactic use, or for community-onset or healthcare-associated infections), whether treatment was empiric or targeted, and quality indicators of antimicrobial prescribing were collected. Compliance to institutional guidelines was only reported for empiric use and surgical prophylaxis. Quality indicators of antimicrobial use considered documented reason for antimicrobial treatment, and presence of stop/review dates.

The Global-PPS protocol remained consistent over the years with minor changes. In 2018, antivirals other than neuraminidase inhibitors were added. The other changes were described in the supplementary appendix. The study was approved by local institutional review board (DSRB reference: 2015/00015, 2017/01012, 2019/00768, 2020/01045).

Statistical analysis

Comparisons of proportions for binary variables were performed using chi-squared test for trend in proportions where appropriate. The median of continuous variables was compared using the Kruskal-Wallis test. A *P*-value of < 0.05 was used as the level of significance. The statistical tests were performed using R software version 3.5.0.

Results

The Global-PPS dataset from 2015 and 2017–2020 included all acute inpatient wards. The median number of available beds on survey day annually was 1357 (range, 1135–1375). The median number of patients admitted was 1173 (range, 1150–1214). The median number of adult wards surveyed annually was 44 (range 35–50). There was a median of 780 (range 755–839) antimicrobial prescriptions on the survey day. Antibacterials for systemic use, corresponding to World Health Organization anatomical therapeutic chemical (WHO ATC) code J01, accounted for 84% of total prescriptions with a median of 665 (range 615–727) on survey day. Antimycotic (ATC code J02) prescriptions accounted for 2% of total prescriptions with a median of 18 (range 11–20) prescriptions, antimycobacterials (ATC code J04) accounted for 6% of total prescriptions with a median of 50 (range 21–52) on survey day. Intestinal anti-infectives (ATC code A07A) and antivirals for systemic use (ATC code J05) accounted for 1% and 7% of total prescriptions and median of 6 (range 1–14) and 70 (range 8–83) prescriptions on survey day. Overall, the mean prevalence of patients on antimicrobials was 49% (range, 45–55%) and varied significantly over the years. It has reduced from 55% in 2015 to 49% in 2019 and 47% in 2020 (p-value of test for trend in proportions = 0.02). Similar trends were observed in terms of antibacterials for systemic use (ATC code J01) from 54% in 2015 to 45% in 2019 and 42% in 2020, p-value of test for trend in proportions < 0.01. (Table 1)

Table 1
Antimicrobial use in inpatients from 2015 to 2019

Year	2015	2017	2018	2019	2020	P
No. of available beds						
No. of patients admitted	1018	1150	1173	1214	1182	NA
No. of patients on antimicrobials	558 (55%)	519 (45%)	592 (50%)	589 (49%)	558 (47%)	0.02
No. of patients on antibacterials for systemic use (J01)	550 (54%)	504 (44%)	562 (48%)	550 (45%)	501 (42%)	< 0.01
Age, median years (range)	73 (16–99)	69 (17–100)	71 (17–100)	72 (15–99)	71 (16–101)	-
Male	290 (53%)	281 (54%)	340 (57%)	345 (59%)	330 (59%)	-
No. of antimicrobials	768	755	839	821	780	-
Antibacterials for systemic use (J01)	727 (95%)	647 (86%)	692 (82%)	665 (81%)	615 (79%)	-
Antimalarials (P01BA)	0	2 (0.2%)	0	10 (1%)	4 (0.5%)	-
Antimycobacterials (J04)	21 (3%)	51 (7%)	50 (6%)	44 (5%)	52 (7%)	-
Antimycotics for systemic use (J02)	11 (1%)	19 (3%)	13 (2%)	18 (2%)	20 (3%)	-
Antivirals for systemic use (J05)	8 (1%)	26 (3%)	80 (10%)*	70 (9%)	83 (11%)	-
Intestinal anti-infectives (A07A)	1 (< 1%)	10 (1%)	4 (< 1%)	14 (2%)	6 (< 1%)	-

P = test for trends in proportions and test for differences in median using the Kruskal-Wallis test as appropriate.

*Introduction of the surveillance of the complete list of antivirals for systemic use (J05) as opposed to surveillance of neuraminidase inhibitors (J05AH) alone in 2015 and 2017.

Overall, the prevalence of patients on antimicrobials was reducing but not significantly different in the medical (56% in 2015 to 47% in 2020) and haematology-oncology wards (73%, 2015 to 66%, 2020). The proportion of patients on antimicrobials increased significantly in the surgical wards 49%, 2015 to 58%, 2020). In intensive care wards, proportion of patients on antimicrobials decreased from 2015 to 2018 but increased to a high of 81% in 2019. In 2020, antimicrobial use in the infectious disease wards which housed suspected or confirmed COVID-19 cases was 29%. (Table 2)

Table 2
Patients on antimicrobials divided by ward types from 2015 to 2020.

Year	2015	2017	2018	2019	2020	P
Overall	558/1018 (55%)	519/1150 (45%)	592/1173 (50%)	589/1214 (49%)	558/1182 (47%)	0.02
Medical ward	331/596 (56%)	335/780 (43%)	404/852 (47%)	395/860 (46%)	372/789 (47%)	0.08
Surgical ward	168/341 (49%)	133/281 (47%)	139/244 (57%)	151/285 (53%)	76/130 (58%)	0.03
Intensive care ward	32/44 (73%)	30/51 (59%)	23/41 (56%)	26/32 (81%)	34/44 (75%)	0.18
Haematology and Oncology Ward	27/37 (73%)	21/38 (55%)	26/36 (72%)	17/37 (46%)	23/35 (66%)	0.34
Infectious disease ward	-	-	-	-	53/184 (29%)	-

P = test for trends in proportions.

Over the years, common indications for antimicrobial use were community acquired infections (47–63%) and healthcare-associated infections (26–39%). The top reasons for starting antibiotics were pneumonia or lower respiratory tract infections (26–34%), skin and soft tissue infections (11–15%), intra-abdominal infections (9–10%), lower urinary tract infections(4–12%), and upper urinary tract infections (3–13%) (Table 3).

Table 3
Indications of antimicrobials use and top 10 reasons to treat inpatients with at least one antibiotic for systemic use (J01), year 2015–2020

Year	**2015**	**2017**	**2018**	**2019**	**2020**
	No. of antimicrobials				
Type of indication	768	755	839	821	780
Community acquired infections	482 (63%)	353 (47%)	500 (60%)	487 (59%)	444 (57%)
Healthcare associated infection	227 (30%)	295 (39%)	245 (29%)	212 (26%)	247 (32%)
Medical prophylaxis	8 (1%)	30 (4%)	37 (4%)	35 (4%)	42 (5%)
Surgical prophylaxis	36 (5%)	34 (5%)	26 (3%)	26 (3%)	27 (4%)
Unknown indication	13 (2%)	39 (5%)	23 (3%)	28 (3%)	13 (2%)
Others (e.g. use as prokinetic)	2 (< 1%)	4 (1%)	8 (1%)	33 (4%)	7 (1%)
	No. of patients				
Top 10 diagnosis	550	504	562	550	501
Pneumonia or lower respiratory tract infection	184 (34%)	142 (29%)	144 (26%)	150 (27%)	144 (29%)
Skin and soft tissue infections†	81 (15%)	54 (11%)	61 (11%)	75 (14%)	66 (13%)
Intra-abdominal infections‡	54 (10%)	47 (9%)	55 (10%)	49 (9%)	44 (9%)
Upper urinary tract infections§	28 (5%)	14 (3%)	61 (11%)	48 (9%)	65 (13%)
Lower urinary tract infections (cystitis)	44 (8%)	58 (12%)	44 (8%)	36 (7%)	20 (4%)

Patients recorded with more than one diagnosis were counted by number of diagnoses.

Patients not treated with antibiotics for systemic use, but who were treated with other antimicrobials (e.g., antimalarials) were not included

†Includes cellulitis, wound infections (including surgical site infections), deep soft tissue infections not involving bone (eg, infected pressure or diabetic ulcers, abscesses). ‡Includes intra-abdominal sepsis and hepatobiliary and intra-abdominal abscesses. §Includes catheter-related urinary tract infections and pyelonephritis.

**Includes septic arthritis (including prosthetic joints) and osteomyelitis.

††Includes sepsis syndrome or septic shock with no clear anatomical site.

Year	2015	2017	2018	2019	2020
Gastrointestinal infections	16 (3%)	23 (5%)	21 (4%)	24 (4%)	21 (4%)
Unknown	8 (2%)	36 (7%)	26 (5%)	21 (4%)	10 (2%)
Bone and joint infections **	12 (2%)	14 (3%)	19 (3%)	22 (4%)	17 (3%)
Acute Bronchitis or exacerbations of chronic bronchitis	10 (2%)	15 (3%)	17 (3%)	17 (3%)	6 (1%)
Sepsis ††	19 (4%)	23 (5%)	12 (2%)	15 (3%)	8 (2%)
Patients recorded with more than one diagnosis were counted by number of diagnoses.					
Patients not treated with antibiotics for systemic use, but who were treated with other antimicrobials (e.g., antimalarials) were not included					
†Includes cellulitis, wound infections (including surgical site infections), deep soft tissue infections not involving bone (eg, infected pressure or diabetic ulcers, abscesses). ‡Includes intra-abdominal sepsis and hepatobiliary and intra-abdominal abscesses. §Includes catheter-related urinary tract infections and pyelonephritis.					
**Includes septic arthritis (including prosthetic joints) and osteomyelitis.					
††Includes sepsis syndrome or septic shock with no clear anatomical site.					

Forty-seven different systemic antibacterials were used in patients admitted to adult wards on the survey days. The penicillins were the most prescribed class (1562/3346 antibacterial prescriptions, 47%), comprising mainly amoxicillin with beta-lactamase inhibitor (1125/3346, 34%) and piperacillin with beta-lactamase inhibitor (300/3346, 9%). The second and third most prescribed antibacterials were cephalosporins (462/3346 ,14%) - mainly cefazolin, ceftriaxone, and fluoroquinolones (355/3346, 11%)- mainly ciprofloxacin and levofloxacin. The overall antibacterial utilisation trends were stable since 2015 (Fig. 1). Amoxicillin with beta-lactamase inhibitor proportion increased from 28.2% in 2015 to 37.0% in 2017, then decreased to 36.1% in 2019 and 34.8% in 2020. Piperacillin with beta-lactamase inhibitor proportion was on downward trend from 10.7% in 2015 to 9.2% in 2019 and 7.0% in 2020. Meropenem increased from 3.9% in 2015 to 5.1% in 2019 and 7.6% in 2020. Carbapenems increased from 5.1% in 2015 to 9.3% in 2017, then decreased to 5.9% in 2019 and 8.8% in 2020. Ciprofloxacin proportion changed from 8.3% in 2015 to 9.3% in 2019 and 5.0% in 2020.

For quality indicators, there was an overall improvement in terms of documented reasons for giving antimicrobials in the medical records: 91% in 2015 to 94% in 2019 and 97% in 2020 (p-value of test for trend in proportions < 0.01). The documentation of stop/review date improved from 53% in 2015 to 56% in 2019 and 61% in 2020 (p-value of test for trend in proportions < 0.01). Compliance to guideline did not change significantly from 71% in 2015 to 62% in 2019 and 73% in 2020 (p-value of test for trend in proportions = 0.08). The proportion of surgical antimicrobial prophylaxis prescriptions being ordered for more than 1 day did not significantly decrease over time: 56% in 2015 to 69% in 2019 and 52% in 2020 (p-value of test for trend in proportions = 0.76). (Table 4)

Table 4
Empiric antimicrobial use and prescribing quality indicators from 2015 to 2020

Year	2015	2017	2018	2019	2020	P
No. of anti-microbials	768	755	839	821	780	-
Empiric treatment	608 (79%)	538 (71%)	660 (79%)	577 (70%)	532 (68%)	-
Reasons in notes	697 (91%)	733 (97%)	746 (89%)	772 (94%)	755 (97%)	< 0.01
Stop/review date	404 (53%)	323 (43%)	450 (54%)	458 (56%)	476 (61%)	< 0.01
Guideline compliant[a]	340/479 (71%)	291/375 (78%)	286/403 (71%)	235/377 (62%)	248/344 (73%)	0.08
No guideline available	96/589 (16%)	66/480 (14%)	138/560 (25%)	108/507 (21%)	110/463 (24%)	-
Surgical prophylaxis > 24 hours	20/36 (56%)	20/34 (59%)	11/26 (42%)	18/26 (69%)	15/27 (52%)	0.76

[a]The number of antimicrobial prescriptions for which guidelines were available was used as the denominator to calculate percentages. Only includes empiric and surgical prophylaxis use. P = test for trends in proportions.

The number of courses of carbapenems, piperacillin-tazobactam and ciprofloxacin reduced by 17% from 7046 during the 6-month period from July to December 2019 to 5852 during the next 6-month period from January to June 2020. However, the proportion of courses reviewed by AMS team were maintained at 4834/7046 (69%) compared to 4141/5853 (71%). The number of recommendations made and accepted were also maintained during both periods, 1151/1440 (80%) vs. 1204/1537 (78%).

Discussion

Despite the re-deployment of our AMS manpower, the prevalence of antimicrobials and antibacterials have shown reduction from 2015 to 2020 despite the COVID-19 pandemic. In 2020, about a quarter of patients in the infectious disease wards were on antimicrobials. Among the antibacterials audited via prospective review and feedback, only meropenem showed an increase. However, this trend started before the pandemic. Overall, antimicrobial prescribing quality indicators continued to improve or remained stable. Our audit using Global PPS methodology found that only 29% of patients with suspected or confirmed COVID-19 were on antibacterial agents. This is in stark contrast to 71.9%, reported by Langford et al in a recently published meta-analysis and 71% reported by Nori et al during the March to May pandemic surge period in New York.[8, 9] This may be accounted by rapid confirmatory diagnosis of SARS-CoV-2 infection as the cause of pneumonia in our setting, and the vast majority of patients having non-severe infections.[10] To prepare for the pandemic, the AMS team was requested by the hospital management to work with hospital pharmacy to provide recommendations on alternative antimicrobial use in anticipation of possible shortfall. In addition, the team briefed the hospital senior management on the possibilities of antibiotic supply disruption and shared on common inappropriate use that was previously observed during audit and feedback. These case examples were created into monthly messages and disseminated to all doctors and pharmacists via email. It is possible that these activities reminded the prescribers on the ground to be more judicious in antimicrobial use.

The sustainable culture of judicious antimicrobial use was developed over the years at our institutions. This could have contributed to continued practice of appropriate prescribing. Since 2009, our multi-disciplinary AMS programme introduced guidelines and performed prospective review and feedback. These measures were augmented by computerised clinical decision support systems (introduced in 2011) and educational efforts to engage healthcare providers and the public on appropriate use of antimicrobials.[11–13] Results of the PPS were shared with the hospital management and senior doctors to raise awareness on the high prevalence of antimicrobial prescribing. These activities may have driven the improvement in some antimicrobial prescribing quality indicators and reduced the prevalence of antimicrobials among acute inpatients. Collectively, the AMS efforts over the years could have paid dividends during the time of COVID-19. The maturity of antimicrobial prescribing habits may have sustained the practices even when AMS resources were substantially reduced.

While the AMS team reduced in size, the team continued prospective review and feedback during the pandemic, focussing on meropenem, piperacillin-tazobactam and oral ciprofloxacin use. The smaller team of pharmacists and physicians maintained the review rate of these antibiotics and provided comparable number of recommendations with similar acceptance rate. Although these constituted a small proportion of the total antimicrobials used, the continued presence of the AMS team and the recommended interventions may have encouraged prescribers to maintain judicious use of antibiotics.

As these were point prevalence studies, the appropriateness of antimicrobial duration and the impact of duration of therapy on antimicrobial utilisation were not reported. The compliance to guidelines was assessed solely based on the prescribing doctor’s documented diagnosis or reasons of use.

Conclusion

As COVID-19 diverted resources from AMS teams, there was no significant deterioration in trends of antimicrobial use or reduction in quality of antimicrobial prescribing at our institutions. Despite a smaller AMS team, the presence of an established multi-disciplinary AMS programme prior to the COVID-19 pandemic managed to keep antimicrobial prevalence and quality of antimicrobial prescribing stable in our institutions. As the pandemic continues, attention must be given to control the amount and appropriateness of antimicrobial use. AMS resources and efforts should be enhanced especially in areas where AMS practices are still in early stages of development. As the global momentum of controlling antimicrobial resistance accumulate in last few years, careful and deliberate actions must be taken now so that the COVID-19 pandemic does not derail this process.

List Of Abbreviations

Coronavirus disease 2019 (COVID-19)

Antimicrobial stewardship (AMS)

Tan Tock Seng Hospital (TTSH)

National Centre for Infectious Diseases (NCID)

Full-time equivalent (FTE)

Infectious diseases (ID)

Global Point Prevalence Survey (Global-PPS)

Declarations

Ethics approval and consent to participate

The study was approved by local institutional review board (DSRB reference: 2015/00015, 2017/01012, 2019/00768, 2020/01045).

Consent for publications

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors have no conflict of interests to declare.

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This study was conducted as part of our routine work.

Authors’ contributions

DC, TH, TM conceptualise the study design. TM wrote the manuscript draft with input from all authors. ST performed the data analysis. SH, HL, MY, BH, CB, SH, TM collected all the data

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Figures

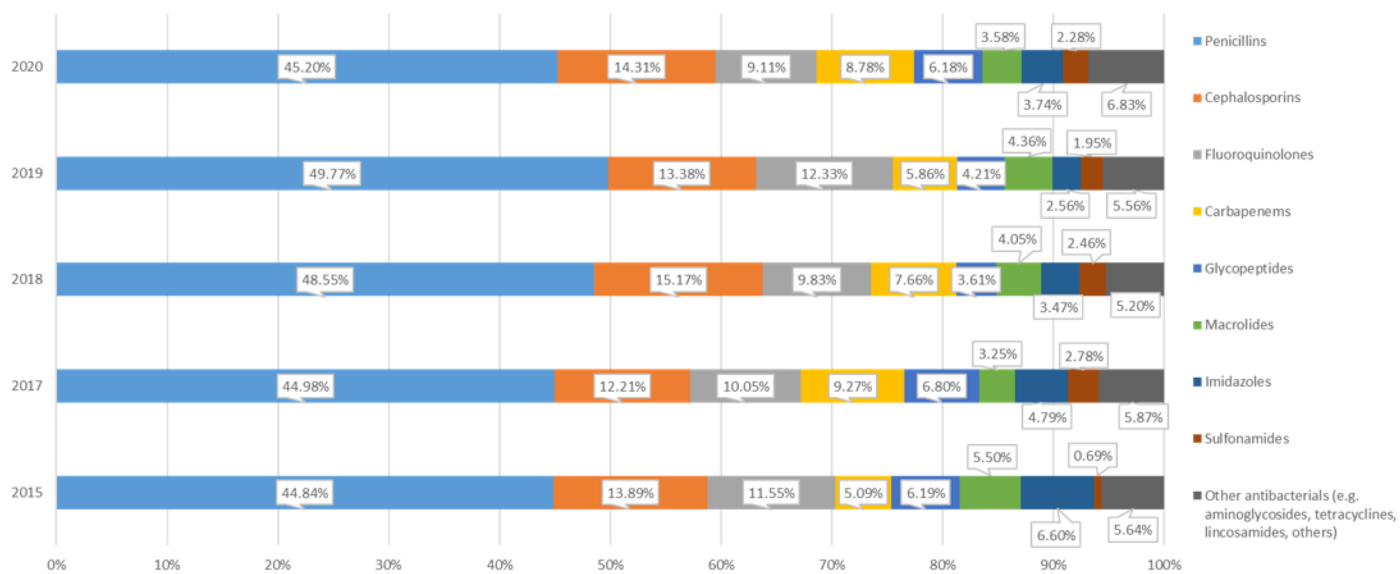

Figure 1

Anti-bacterial use from 2015 to 2020